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Asymmetric Conjugate Addition of Alkylzirconium Reagents to α,β-Unsaturated Lactones

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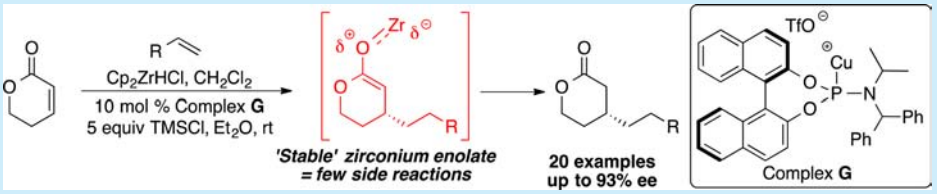
Supporting Information



ABSTRACT: The asymmetric synthesis of β-substituted lactones by catalytic asymmetric conjugate addition of alkyl groups to α,β-unsaturated lactones is reported. The method uses alkylzirconium nucleophiles prepared in situ from alkenes and the Schwartz reagent. Enantioselective additions to 6- and 7-membered lactones proceed at rt, tolerate a wide variety of functional groups, and are readily scalable. The method was used in a formal asymmetric synthesis of mitsugashiwalactone.

The development of Cu-catalyzed asymmetric conjugate addition (ACA) reactions to α,β-unsaturated carbonyl derivatives has received tremendous attention for over 25 years. This work has led to a number of highly enantioselective methods,[1] and a few of these are now so sufficiently robust that they can be used in complex molecule synthesis.[1e,2] These reactions have for the most part been developed with a small number of model substrates with the major focus on simple linear and cyclic enones,[3,4] and additions to some substrate types are surprisingly underrepresented[1b,4,5] and extensions will require a step change in current asymmetric methodology.

Lactones superficially resemble cyclic ketones but differ in key properties such as conformation and strain energy.[6,7] They are an important substrate class for which generally useful Cu-catalyzed ACA reactions have not been developed. The ACA of alkyl nucleophiles to α,β-unsaturated lactones would directly provide enantiomerically enriched lactones, but development of a broadly useful method has been elusive. As previously pointed out,[8] early methods involve a high catalyst loading,[9] reactions that report only conversion,[10] or a very limited scope.[11] Using dialkylzinc reagents, Hoveyda reported the first effective ACAs to α,β-unsaturated lactones (Figure 1a)[8] and applied this method in the synthesis of clavirolide C.[2e] High yields are observed when the reaction is carried out in the presence of an aldehyde which traps the ACA product as an aldol adduct, and a subsequent retroaldol step is used to release the desired product.[2e,8,12] Hoveyda et al. attribute the low yields observed in the absence of an aldehyde to *adventitious ketene formation or intermolecular Michael addition*.[8] Feringa et al. developed a Grignard based procedure which (Figure 1a)[13] gives high yields under pseudoinfinite dilution conditions, where a solution of lactone is slowly added to a cold solution of the catalyst and nucleophile. Taken together, these two reports suggest that intermolecular

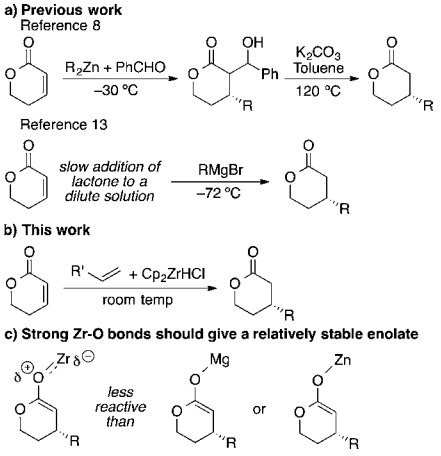


Figure 1. Asymmetric 1,4-addition of alkyl nucleophiles to lactones.

reactions between intermediate enolates and starting lactone need to be suppressed to develop high yielding procedures.

Here, we report a direct method for 1,4-addition of alkyl units to α,β-unsaturated lactones (Figure 1b). We reasoned that strong group IV metal−oxygen bonds (Figure 1c)[14,15] would make zirconium enolates less nucleophilic, and proceeded to examine the ACA of alkylzirconium reagents[2p,16] to lactones. Alkenes, when treated with the Schwartz reagent,[17] undergo hydrometalation to alkylzirconium nucleophiles.[18] Conditions previously used for the addition of 4-phenyl-1-butene **1** to cyclohexenone[16a] were applied to 5,6-dihydropyran-2-one **2a**

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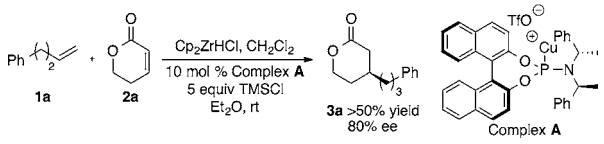
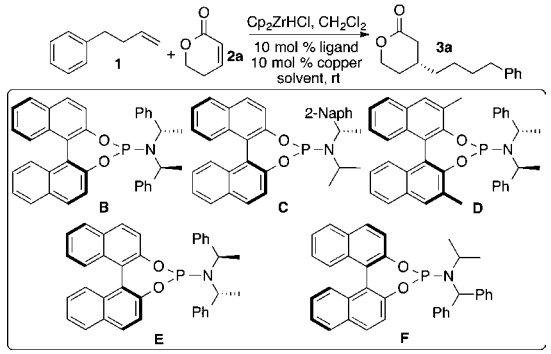
(Scheme 1), and we obtained the 1,4-addition product **3a** with 80% ee and >50% yield as determined by ^{1}H NMR.

Scheme 1. Initial ACA of Alkylzirconiums to Lactones



We examined copper sources in combination with phosphoramidite ligands and solvents (Table 1). Copper sources gave

Table 1. Representative Optimization Reactions[a]



entry	Cu source	ligand	additive	solvent	ee (%)
1	$(CuOTf)_2{\cdot}C_6H_6$	**B**	TMSCl	Et_2O	(*S*)-80
2	$[Cu(MeCN)_4{\cdot}OTf]$	**B**	TMSCl	Et_2O	(*S*)-67
3	$[Cu(MeCN)_4{\cdot}PF_6]$	**B**	TMSCl	Et_2O	0
4	$(CuOTf)_2{\cdot}C_6H_6$	**C**	TMSCl	Et_2O	(*S*)-79
5	$(CuOTf)_2{\cdot}C_6H_6$	**D**	TMSCl	Et_2O	(*S*)-75
6	$(CuOTf)_2{\cdot}C_6H_6$	**E**	TMSCl	Et_2O	(*S*)-55
7	**$(CuOTf)_2{\cdot}C_6H_6$**	**F**	**TMSCl**	**Et_2O**	**(*R*)-89**
8	$(CuOTf)_2{\cdot}C_6H_6$	**F**	–	Et_2O	(*R*)-83
9[c]	$(CuOTf)_2{\cdot}C_6H_6$	**F**	TMSCl	CH_2Cl_2	(*R*)-80
10[c]	$(CuOTf)_2{\cdot}C_6H_6$	**F**	–	–	(*R*)-91
11	$(CuOTf)_2{\cdot}C_6H_6$	**F**	TMSCl	2-MeTHF	(*R*)-86
12	$(CuOTf)_2{\cdot}C_6H_6$	**F**	TMSCl	*t*-BuOMe	(*R*)-88
13	$(CuOTf)_2{\cdot}C_6H_6$	**F**	–	*t*-BuOMe	(*R*)-70
14[b,c]	$AgNTf_2$ + CuCl	**F**	TMSCl	CH_2Cl_2	0
15[b,c]	$AgNTf_2$ + CuCl	**F**	TMSCl	Et_2O	(*R*)-44
16[b,c]	$AgNTf_2$ + CuCl	**F**	–	CH_2Cl_2	(*R*)-93
17[b,c]	$AgClO_4$ + CuCl	**F**	–	Et_2O	(*R*)-89
18[b,c]	$AgClO_4$ + CuCl	**F**	TMSCl	Et_2O	(*R*)-78
19[b,d]	$AgClO_4$ + CuCl	**F**	18-crown-6	CH_2Cl_2	(*R*)-94

[a]Conditions: 4-phenyl-1-butene (2.5 equiv), Cp_2ZrHCl (2 equiv), 5,6-dihydropyran-2-one (1 equiv), copper (10 mol %), Ligand (10 mol %), Additive (5 equiv), rt, >50% yield by crude ^{1}H NMR. [b]Silver (15 mol %), precipitate filtered before use. [c]Less that 10% yield observed. [d]1 equiv of 18-crown-6 was used, and ca. 30% isolated yield was obtained.

vastly different results (from racemic to 80% ee) depending on the counterion and solvating species, with $(CuOTf)_2{\cdot}PhH$ giving the highest *ee* (entry 1). Switching from ligand **B**[19] to 2-naphthyl-substituted **C** had little effect on enantioselectivity (79% ee, Table 1 entry 4); however, an isomer bearing an achiral amine moiety (ligand **F**,[16b] entry 7) appreciably increased the enantioselectivity to 89% ee. Upon looking at different solvents in the presence or absence of TMSCl (entries 7−13), diethyl ether + TMSCl gave the highest level of enantioselectivity (entry 7, 89% ee) with the exception of CH_2Cl_2 (entry 10), which gave 91% ee but without full conversion in this solvent with only a low isolated yield (<10%). Keeping the reaction conditions of entry 7, but varying the temperature (not shown), did not appreciably increase the enantioselectivity. Copper perchlorate and copper triflimidate salts gave excellent enantioselectivity (93% ee, entry 16) in the absence of TMSCl. However, reaction yields with these counterions were always low (<10%) even though full conversion was observed. Extensive attempts to optimize these yields were not fruitful. Although the combination of $(CuOTf)_2{\cdot}PhH$ and **F** gave a slightly lower enantioselectivity (89 vs 93% ee), we could consistently obtain over 75% isolated yield using this system.

We next prepared catalyst complex **G** (Figure 2; see Supporting Information (SI)), composed of CuOTf and ligand

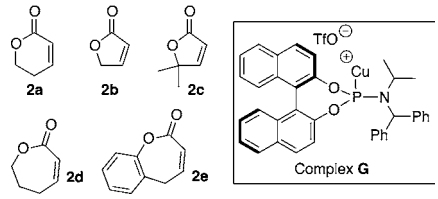


Figure 2. Lactones and catalyst complex used here.

F. This complex is more convenient than $(CuOTf)_2{\cdot}PhH$ and was used for the rest of these studies. **G** is readily made on a >1 g scale, can be weighed out in air, and is stable for at least a month if stored on the bench under argon.

We examined the hydrometalation−ACA of simple alkenes to **2a** (Table 2, entries 1−6). These experiments allowed a comparison to previous methods for ACA to lactones. Simple linear (entries 1−4) and hindered (entries 5 and 6) alkenes are well tolerated. In the case of volatile **3b**, the alkene (ethylene) used is a gas and the hydrozirconation is performed under a balloon atmosphere of ethylene (see SI).

When we examined lactones of different ring sizes and substitution patterns (Figure 2) we found that 5-membered rings are difficult substrates; **2b** was rapidly and completely consumed, and no desired product was recovered, while, conversely, **2c** was recovered unchanged. These conditions are also unsuitable for acyclic α,β-unsubstituted esters. These results, in combination with those obtained using triflimidate and perchlorate salts (Table 1, entries 14−19) suggest that it is the combination of the catalyst and reactive enolate that leads to low yields. When more reactive substrate−catalyst combinations are used (i.e., **2b** or more Lewis acidic catalysts) very low yields are observed, presumably due to enolate attacking lactones activated by the catalyst.[15b] As this system is unsuitable for 5-membered ring substrates, Hoveyda's 1,4-addition/aldol/retroaldol procedure[8] is the only currently viable method for ACA of alkyl units to **2b**. The addition of alkyl groups to 7-membered lactones **2d** and **2e** goes smoothly, with good yields and high enantioselectivities observed (entries 7 and 8).

The use of functionalized nucleophiles in Cu-catalyzed ACAs remains a major challenge,[1b,c,20] and with lactones the previous nucleophile scope is extremely limited (see Figure 3). The use of starting materials incorporating functional groups offers extensive opportunities to further elaborate the products.

We found a range of functional groups could be added (Figure 4). Alkenes bearing aromatic rings (**3a**,**j**,**k**,**m**,**o** and **4b**), internal olefins (**3h**), ethers and protected alcohols (**3i**,**j**,**k**,**l**,**o** and **4b**), stereogenic centers (**3h**,**o**), halogens (**3m**,**o**), multiple structural

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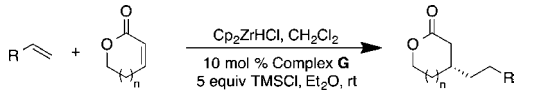
Table 2. Asymmetric Addition of Alkyl Groups[a]



entry	substrate	product	yield[b]	ee[c]
1		3b	53%[d]	92%
2		3c	73%	89%
3		3d	84%	89%
4		3e	70%	88%
5		3f	60%	84%
6		3g	58%	82%
7	2d +	4a	95%	93%
8	2e +	5	63%	88%[e]

[a]Conditions: alkene (2.5 equiv), Cp_2ZrHCl (2 equiv), lactone (1 equiv), complex **G** (10 mol %), TMSCl (5 equiv), Et_20, rt. [b] Isolated yield. [c] Ee determined by derivitization and HPLC; see SI. [d] Volatile. [e] Ee determined directly by HPLC.

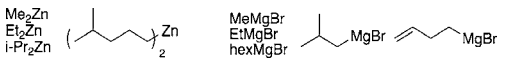


Figure 3. Alkyl nucleophiles previously used in ACA to lactones.

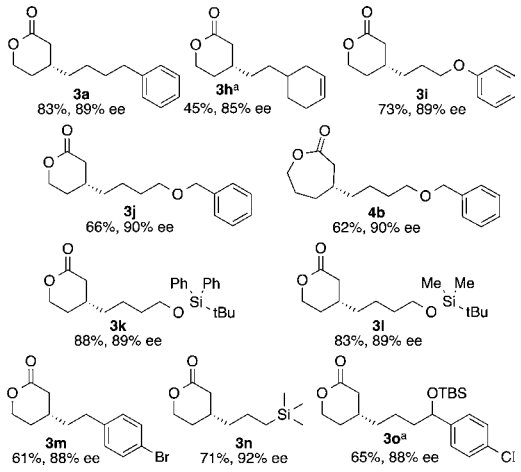
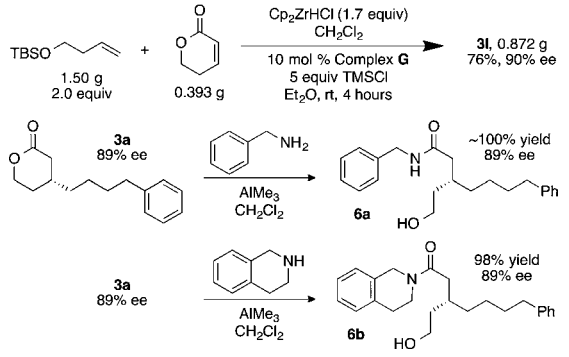


Figure 4. Products obtained by ACA using functionalized alkenes as starting materials. [a] Isolated as a mixture of diastereoisomers.

features (**3o**) and an electron-rich styrene (**3m**) and allylsilane (**3n**) uniformly gave high levels of enantiomeric excess (85−92% ee). All reactions were performed at rt and are typically complete within a few hours.

One possible drawback of the methodology is the use of excess alkene and Schwartz reagent relative to the lactone substrate, and so when we examined the formation of product **3l** (bearing a silyl-protected alcohol) on a preparative scale (Scheme 2) we arbitrarily reduced the ratios of the alkene (to 2 equiv) and Schwartz reagent (to 1.7 equiv). On an 8-mmol scale we obtained 0.872 g of **3l** (76% yield, 90% ee).

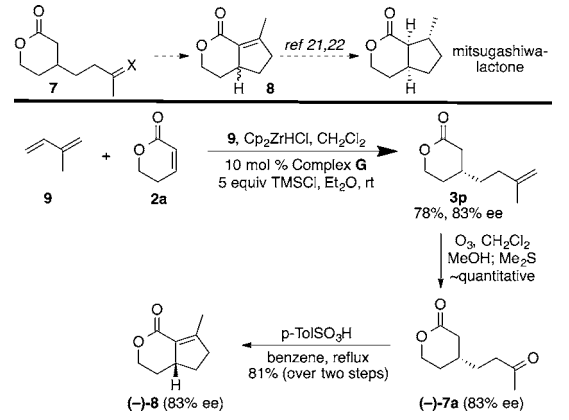
Scheme 2. Preparative Scale and Ring-Opening Reactions



Ring opening of enantioenriched **3a** (89% ee) with primary and secondary amines (Scheme 2) was also examined. Trimethylaluminum mediated ring opening in CH_2Cl_2 gave functionalized amides **6a** and **6b**.

We next prepared a compound previously used in natural product synthesis (Scheme 3). Racemic **8** is a late-stage

Scheme 3. Formal Asymmetric Synthesis of Mitsugashiwalactone



intermediate in the syntheses of *rac*-mitsugashiwalactone.[21,22] Asymmetric syntheses of mitsugashiwalactone have been reported from a chiral pool[23] and enantiomerically resolved materials,[24] but not (to our knowledge) from material where asymmetry is introduced in a catalytic asymmetric approach. Access to **8** represented a much more demanding test of the method than the examples we had examined thus far. We suspected that an appropriately functionalized lactone **7** could be converted to **8** by dehydrative condensation, but the stability of the lactone ring, the stereochemical integrity of the tertiary center during cyclization, and the ability to access **7** were all unclear.

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To synthesize **7**, we chose to investigate the hydrometalation−ACA of isoprene **9** to lactone **2a** (Scheme 3). This conjugated diene, a substrate type that we had not yet examined, showed excellent chemoselectivity between the mono- and disubstituted olefins and gave **3p** with high enantioselectivity at rt on a 6.0 mmol scale (78% yield, 83% ee). Using isoprene as a starting material is attractive because it is readily available and inexpensive. Cleavage of the olefin in **3p** by ozonolysis gave (−)-**7a** quantitatively, and cyclization to (−)-**8** was accomplished using tosylic acid under Dean−Stark conditions (81% yield from **3p**) with no detectable loss of enantiopurity.

In conclusion, a new method has been developed for Cu-catalyzed ACA of alkyl nucleophiles to α,β-unsaturated lactones. The nucleophiles are generated in situ from alkenes and the Schwartz reagent. We applied the method in a formal asymmetric synthesis of mitsugashiwalactone. Our laboratory is currently investigating extensions and applications of alkylzirconium addition reactions.

■ ASSOCIATED CONTENT

Supporting Information

All procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected reviews: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rossle, M. *Synthesis* **2007**, 1279. (b) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (d) Thaler, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 645. (e) Wang, S. Y.; Loh, T. P. *Chem. Commun.* **2010**, *46*, 8694.

(2) Selected examples of Cu-catalyzed ACA in natural product synthesis: (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (b) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841. (c) Alexakis, A.; March, S. *J. Org. Chem.* **2002**, *67*, 8753. (d) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977. (e) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904. (f) Casas-Arce, E.; ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem.—Eur. J.* **2008**, *14*, 4157. (g) Bates, R. W.; Sridhar, S. *J. Org. Chem.* **2008**, *73*, 8104. (h) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 761. (i) Pereira, C. L.; Chen, Y.-H.; McDonald, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 6066. (j) Wang, S.-Y.; Song, P.; Chan, L.-Y.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 5166. (k) Hartmann, E.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6195. (l) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501. (m) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21. (n) Gartner, M.; Qu, J. P.; Helmchen, G. *J. Org. Chem.* **2012**, *77*, 1186. (o) Mak, J. Y. W.; Williams, C. M. *Chem. Commun.* **2012**, *48*, 287. (p) Maksymowicz, R. M.; Roth, P. M. C.; Thompson, A. L.; Fletcher, S. P. *Chem. Commun.* **2013**, *49*, 4211. (q) Endo, K.; Hamada, D.; Yakeishi, S.; Shibata, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 606.

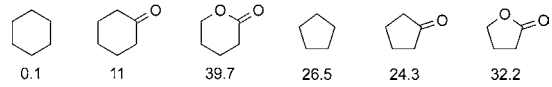
(3) For example more than 4000 relevant asymmetric additions to cyclohexenone have been reported; see ref 4.

(4) Alexakis, A., Krause, N., Woodward, S., Eds. *Copper-Catalyzed Asymmetric Synthesis*; Wiley-VCH: 2014.

(5) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

(6) For example, the 6-membered δ-valerolactone has an overall strain energy that is substantially greater than other 6-ring alicyclic compounds. The 6-membered lactone also has higher strain than the 5-membered lactone by about 7.5 kJ/mol, the reverse order of strain energies generally observed for alicyclic compounds.

Conventional strain-energies (at 298.15K H_m(strain)/KJ/mol)



(7) Luisa, M.; Pilcher, G.; Yang, M. Y.; Brown, J. M.; Conn, A. D. *J. Chem. Thermodyn.* **1990**, *22*, 885.

(8) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306.

(9) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275.

(10) (a) Yan, M.; Zhou, Z. Y.; Chan, A. S. C. *Chem. Commun.* **2000**, 115. (b) Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189. (c) Liang, L.; Yan, M.; Li, Y. M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2575. (d) Naeemi, Q.; Robert, T.; Kranz, D. P.; Velder, J.; Schmalz, H. G. *Tetrahedron: Asymmetry* **2011**, *22*, 887.

(11) (a) Liang, L.; Su, L. M.; Li, X. S.; Chan, A. S. C. *Tetrahedron Lett.* **2003**, *44*, 7217. (b) Feringa, B. L.; Badorrey, R.; Pena, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834. (c) Clavier, H.; Coutable, L.; Guillemin, J. C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921. (d) Rix, D.; Labat, S.; Toupet, L.; Crevisy, C.; Mauduit, M. *Eur. J. Inorg. Chem.* **2009**, 1989.

(12) Csizmadiová, J.; Mečiarová, M.; Almássy, A.; Horváth, B.; Šebesta, R. *J. Organomet. Chem.* **2013**, *737*, 47.

(13) Mao, B.; Fananas-Mastral, M.; Feringa, B. L. *Org. Lett.* **2013**, *15*, 286.

(14) It is well established that Zr−O single and Zr═O double bonds in relevant zirconcene complexes are anomalously short, reflecting a significant ionic contribution. See ref 15.

(15) Isolatable zirconium ester enolates have been characterized, and their ability to initiate polymerization was studied in detail by the Chen group: (a) Howard, W. A.; Parkin, G. *J. Am. Chem. Soc.* **1994**, *116*, 606. (b) Zhang, Y.; Ning, Y.; Caporaso, L.; Cavallo, L.; Chen, E. Y. X. *J. Am. Chem. Soc.* **2010**, *132*, 2695.

(16) (a) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nat. Chem.* **2012**, *4*, 649. (b) Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7995. (c) Maksymowicz, R. M.; Sidera, M.; Roth, P. M. C.; Fletcher, S. P. *Synthesis* **2013**, *45*, 2662. (d) Roth, P. M. C.; Sidera, M.; Maksymowicz, R. M.; Fletcher, S. P. *Nat. Protoc.* **2014**, *9*, 104.

(17) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B. *Org. Synth.* **1993**, *71*, 77.

(18) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Sebesta, R. *ChemCatChem* **2013**, *5*, 1069.

(19) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.

(20) Howell, G. P. *Org. Process Res. Dev.* **2012**, *16*, 1258.

(21) Saeki, M.; Toyota, M. *Heterocycles* **2011**, *82*, 1705.

(22) (a) Liang, K.-W.; Chandrasekharam, M.; Li, C.-L.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 7289. (b) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297.

(23) (a) Takacs, J. M.; Myoung, Y. C. *Tetrahedron Lett.* **1992**, *33*, 317. (b) Weinges, K.; Ziegler, H. J.; Maurer, W.; Schmidbauer, S. B. *Liebigs Ann. Chem.* **1993**, 1029. (c) Takacs, J. M.; Myoung, Y.-C.; Anderson, L. G. *J. Org. Chem.* **1994**, *59*, 6928. (d) Nangia, A.; Prasuna, G. *Tetrahedron* **1996**, *52*, 3435.

(24) Yamane, T.; Takahashi, M.; Ogasawara, K. *Synthesis* **1995**, 444.